ABBOTT

Corporate Regulatory Science

Abbott Laboratories

D-387, Building AP6C
100 Abbott Park Road
Abbott Park, IL 60064-6091

November 12, 1999

The Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane Room 1061
Rockville, MD 20857

RE: Comments on the FDA's Draft Guidance for Industry on ANDA's: Blend Uniformity Analysis [Docket No. 99D-2635]

Dear Sirs or Madams:

Abbott Laboratories submits the following remarks in response to the Agency's request for comments on the above-named subject and docket. Abbott is an integrated worldwide manufacturer of healthcare products employing more than 56,000 people and serving customers in more than 130 countries.

The scientific justification of the need for routine blend uniformity analysis is subject to debate within the pharmaceutical industry. In light of FDA's desire to base regulation upon scientific principle, it is questionable why a draft guidance on this topic would be proposed by the FDA before the scientific foundation has been cast. Blend Uniformity Testing is the number one research project identified for the Drug Product Technical Committee (DPTC) within the Product Quality Research Institute (PQRI) with the goals of establishing this scientific foundation through careful literature review and statistically controlled experimentation. As the results of this PQRI project will be forthcoming in the near future, it is suggested that the FDA consider these results of PQRI before finalizing any guidances pertinent to blend uniformity.

The following issues with the draft guidance are being addressed by the PQRI DPTC:

Sampling Size and Procedures

- Are the known errors associated with blend sampling methods/techniques (1-10) significant enough to bias the results and make the Blend Uniformity Analysis (BUA) inappropriate for routine lot release testing?

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- Can routine tablet uniformity testing be adequate (with modifications if necessary) to assess the potential of the process to produce uniform dosing to the patient?

Equipment Issues

- Can a decision tree (similar to that proposed by Lai (11), and/or VanDen Bergh (12)) or matrices (proposed by JR Johanson-attached) be adapted to help determine appropriate types of blending equipment?

  Proper blender selection is an integral part of process development and should be verified when the technology is transferred to production scale. This is supported by the 1994 FDA Guide to Inspections of Oral Solid Dosage Forms Pre/Post Approval Issues for Development and Validation:

  > *"The major advantage of blend analysis (from a uniformity perspective) is that specific areas of the blender which have greatest potential to be non-uniform can be sampled."*

  Therefore, it is not supportable to perform BUA from blenders (such as diffusion type blenders) that are not known to have "deadspots."

  Testing for the adequacy of mixing to assure uniformity and homogeneity (211.110(a)(3)) would only appear to be "appropriate" if the process cannot be validated or less than optimal equipment has been chosen.

The following issues with the draft guidance could fit within the scope of PQRI DPTC:

- Is BUA an appropriate routine in-process test when ICH and other compendia have not adopted it as such?
- Are two-tier acceptance criteria applicable as is allowed by USP for dosage form uniformity testing?
- Has sampling been adequately investigated to support unit dose sampling for semi-solid states such as softgel suspensions and suppositories?

For reference, the following are excerpts from the DPTC Blend Uniformity Project:

PQRI Questions to be Asked:

(1) Blend Uniformity is tested during process validation studies--is it then necessary to test for blend uniformity for every production batch?

(2) What are the most appropriate test methods for assessing blend uniformity?

(3) Are there new methods that do not alter composition of a powder blend during "unit dose" sampling procedures?

Abbott Laboratories appreciates the opportunity to comment on FDA drafts.

Yours truly,

Frank Pokrop
Director, Corporate Regulatory Science
(847) 937-8473
FAX: (847) 938-3106

cc: Devinder S. Gill (HFD-623)
R. Poska, Abbott

Attachments

References:

1. Allen and Khan, "Critical Evaluation of Powder Sampling Procedures", The Chemical Engineer, May, 1970.
2. Harwood and Ripley, "Errors Associated with the Thief Probe for Bulk Powder Sampling", Journal of Powder & Bulk Solids Technology
3. Garcia, Elsheimer, and Tarczynski, "Examination of Components of Variance for a Production Scale, Low Dose Powder Blend and Resulting Tablets", Drug Development and Industrial Pharmacy, 21(18),2035-2045 (1995).
4. Carstensen and Dali, "Blending Validation and Content Uniformity of Low-Content, Noncohesive Powder Blends", Drug Development and Industrial Pharmacy, 22(4), 285-290 (1196).
5. Berman and Planchard, "Blend Uniformity and Unit Dose Sampling", Drug Development and Industrial Pharmacy, 21(11), 1257-1283 (1995).
6. PDA Technical Report No.25, Blend Uniformity Analysis: Validation and IN-Process Testing, 8/21/97.
7. Perry's Chemical Engineering Handbook, 6th Edition, Chapter 21-3.
8. Lantz and Schwartz, Pharmaceutical Dosage Forms: Tablets Vol. 2, p. 30
9. Carstensen and Rhodes, "Sampling in Blending Validation", Drug Development and Industrial Pharmacy, 19(20), 2699-2708 (1993).
10. Pierre Gy's Sampling Theory and Sampling Practice, Chapter 13
11. Lai, "A Prototype Expert System for Selecting Pharmaceutical Powder Mixers", Pharm Tech, August 1988, pp. 22-31.
12. Van Den Bergh, "Removing the Uncertainty in Solids Mixer Selection", Chem Eng, 1994, 101 (12) 70-77.

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How To Acquire Powder & Bulk Solids Handling Technology Using Indices

By

Dr. J.R. Johanson and
B.D. Cox, JR Johanson, Inc.

Blender Selection Based on Material Properties

By Dr. Jerry R. Johanson

Some materials will blend in almost any type of blender. Blender selection in this case is elementary. You can't go wrong. Other materials drastically restrict blender choices.

There are two essentials for a blender to work satisfactorily. First, it must provide velocity gradients in the solids that act over the entire bulk material and create mixing. Obviously, if material passes through the blender as a rigid plug or even if chunks of the solid are undisturbed, poor mixing results. Second, the blender must not allow the solids to demix or segregate. This is especially critical for mixtures of different particles sizes, densities, surface friction, cohesions, permeability or compressibility.

This paper discusses the solids properties that affect blending and provides some quantitative decisions based on the Johanson Indices characterization of bulk solids.

Bulk Solids Characterization

A series of eight indices[1] characterizes bulk solids flow properties:

Arching Index (AI) This index is the minimum conical outlet diameter (feet) required to prevent solids arching in a mass-flow conical hopper with typical impact pressures from solids' filling. In blenders, it also predicts the size of chunks that might occur in rotating shell blenders and the tendency of solids to demix.

Ratholing Index (RI) This index is essentially the critical rathole diameter in feet for a typical funnel-flow bin or mixer. The index is used to design funnel-flow or partial mass-flow bins where the lower hopper is steep enough to provide mass-flow and the upper hopper is funnel-flow (no flow at the walls). In large, rotating shell blenders, the index predicts the cohesion of solids at the bottom of the mixer and the tendency to form cohesive chunks.

Hopper Index (HI) This single number provides recommended mass-flow hopper angles for various hopper configurations (see Table I). For example, a conical hopper angle (measured from the vertical), must be less than or equal to HI in degrees to produce reliable mass-flow. With the aid of the tables, you can design the other hoppers presented. This index is especially important if the blender must discharge in mass-flow (flow at the walls). Mass-flow can be critical

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[1] Johanson, J.R. **Bulk Solids Flow Indices: A simplified evaluation system.** 1991.

for any blender that does not have active internal agitation during discharge.

Chute Index (CI) This index is the recommended chute angle to prevent material buildup at solids impact areas. This has application to blender discharge chutes.

Flow Rate Index (FRI) This index is the limiting or the unassisted free-fall, gravity flow rate in a conical mass-flow hopper with a one-foot outlet for a totally deaerated solid. Use Figure 1 as a guide for other outlet diameters and configurations. As with the other indices, this single point index is only a guide or an approximation. The FRI also estimates flow rates from slot type hopper outlets of width B and length L by multiplying the flow rate on the graph by 1.3 L/B. You can obtain higher rates than those predicted in Figure 1 if air in injected into the solids or retained during handling. The flow rates cannot exceed the limiting flow rate given in Figure 2.[2] This index also indicates the fluidization potential of a material in a blender.

Density Index (FDI and BDI) Two densities characterize solids. The first, FDI, represents the density at typical hopper outlets and feeders. The second, BDI, represents the density inside a typical bin. They are used to calculate blender, feeder and bin capacities.

Springback Index (SBI) This is the percentage springback when solids are released from solids contact storage pressures to the lower pressures at hopper outlets. This index gives an indication of a solid's elastic windup tendencies. If SBI is larger than 3, we recommend running elastic springback strength tests in addition to standard strength measurements. You likely have a material that will hang up in funnel-flow bins even if the standard RI and AI indices are small. Shredded plastic foam, wood chips, mica, pulp, cotton linters and elastomer pellets often have this problem.[3]

Knowing the various mixing component indices provides a useful guide to determine the success or failure of specific mixers. The next section evaluates various mixers using the indices.

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[2]Johanson, J.R. Method of Calculating Rate of Discharge from Hoppers and Bins. Transactions of SME 232: 69-80, 1965.

[3]Johanson, J.R. Bin and Feeder Design for Wood Chips and Other Springy Bulk Solids. "Proceedings Powder and Bulk Solids," Chicago, IL

Most mixers will satisfy the first requirement of velocity gradients (at least for some materials) or they would not be on the market. The demixing aspect, however, is both material and mixer dependent and at times, affects all mixers.

Demixing in Blenders

Four types of demixing commonly occur in blenders: sifting, angle or repose, fluidization and air currents. In this section, I discuss each of these mechanisms relative to blenders types, material properties likely to affect demixing, and using the indices, identify troublesome solids or solids modifications that may reduce or eliminate the problem.) The various types of demixing and materials descriptions are summarized in Table II.

Sifting

Sifting as a demixing mechanism is caused by fines sifting through a predominantly coarser solid. This demixing occurs whenever the major component features large, free-flowing particles and the minor component is less than one-third of the major component and also free-flowing. Demixing will occur whenever the mixer imposes interparticle motion. Consequently, all batch blenders have this potential. Continuous blenders may have start-up and end-effect demixing. This type of demixing can be reduced by making the major and minor particles the same size or even by making the major component smaller than the minor component. Another approach is to cause the fine minor components to adhere to the larger particles by adding liquid to the coarser particles or introducing a fine, cohesive component in the mixture. Sometimes the natural cohesions associated with the fines component will be sufficient to reduce demixing. The flow indices help quantify these effects (see Table III).

Angle of repose

This form of demixing occurs whenever solids slide on themselves during the mixing action. The material with the steeper angle holds back and allows the less steep repose angle material to slide freely to the bottom of the slope or pile. The initial filling or emptying of all blenders may cause some demixing with this mechanism. Rotating shell-type blenders are especially susceptible to this mechanism and if it is prevalent, you will often find layers of coarse and fines in the blender even after long mixing times. Adding liquid or cohesives to the fines may make the problem worse. Premixing liquid with the coarse before adding the fines reduces fines demixing by causing them to stick to the coarse.

Fluidization

This demixing mechanism occurs when the mixture contains a major free-flowing, fine component that easily fluidizes and a relatively coarse, heavy minor component that easily penetrates the fluidized fines. The fluidization mechanism is especially active in air blenders, rotary plough blenders and high-speed ribbon blenders. Anything that reduces fines fluidization will reduce this demixing. Lowering blender speed, reducing air, adding liquid to the mixture (even in small amounts) and preagglomerating fines fractions all help.

Air currents

Demixing occurs when superfines become airborne by the mixing action. These superfines migrate to the free mixer walls or toward the dust collection system. The quantity of solids involved is usually only a few percent of the total. However, if the superfines are a minor ingredient of the mix, the migration can be significant. Any moisture addition, especially if deposited in a fine spray during the mixing, will suppress the airborne fines. In a multiple component mixture, adding a liquid to the coarse before introducing the super fines to the mixer will cause the superfines to stick to the coarse and not become airborne. This mechanism is especially active in rotary plough and air blenders.

Table III provides a general rating of blenders relative to the various demixing mechanisms and indicates some possible solutions. These are general indications and details on individual mixers may modify the indications in the table.

Material Properties Influences on Velocity Gradients

The ability of a mixer to produce mixing velocity gradients is highly dependent on the mixer design details and requires a detailed analysis of the specific mixer. This section contains a few general guidelines and a specific evaluation of a typical rotary shell blender.

In general, excessive cohesive strength as indicated by large AI or RI decreases the blender's effectiveness in producing the necessary velocity gradients. For example, a cohesive solid in a rotating shell, ribbon or screw mixer may form globs that never mix. A very slight cohesion can block the tubes of a gravity flow tube blender or even more subtly stop flow at the blender walls, leaving large pockets of unblended solids. A large rathole index will cause an air blender to blow holes in the mixture, leaving large portions undisturbed or unmixed.

Extremely low flow rate index (FRI) materials will fluidize in a screw mixer without being moved or lifted by the screw. Materials with a low hopper index (HI) will likely discharge from a rotating shell in a funnel-flow pattern, thereby increasing the demixing problems in gravity flow blenders and leaving large unblended solids portions. Table IV gives general ratings of various blenders for different types of materials characterized by the indices numbers given. The ratings take into account both demixing and velocity gradient considerations. In each case there may be special blender designs that improve the blender's performance beyond that indicated. Some specific designs may also perform worse than indicated. You should use the table only a general guideline. Specific blenders require specific analyses.

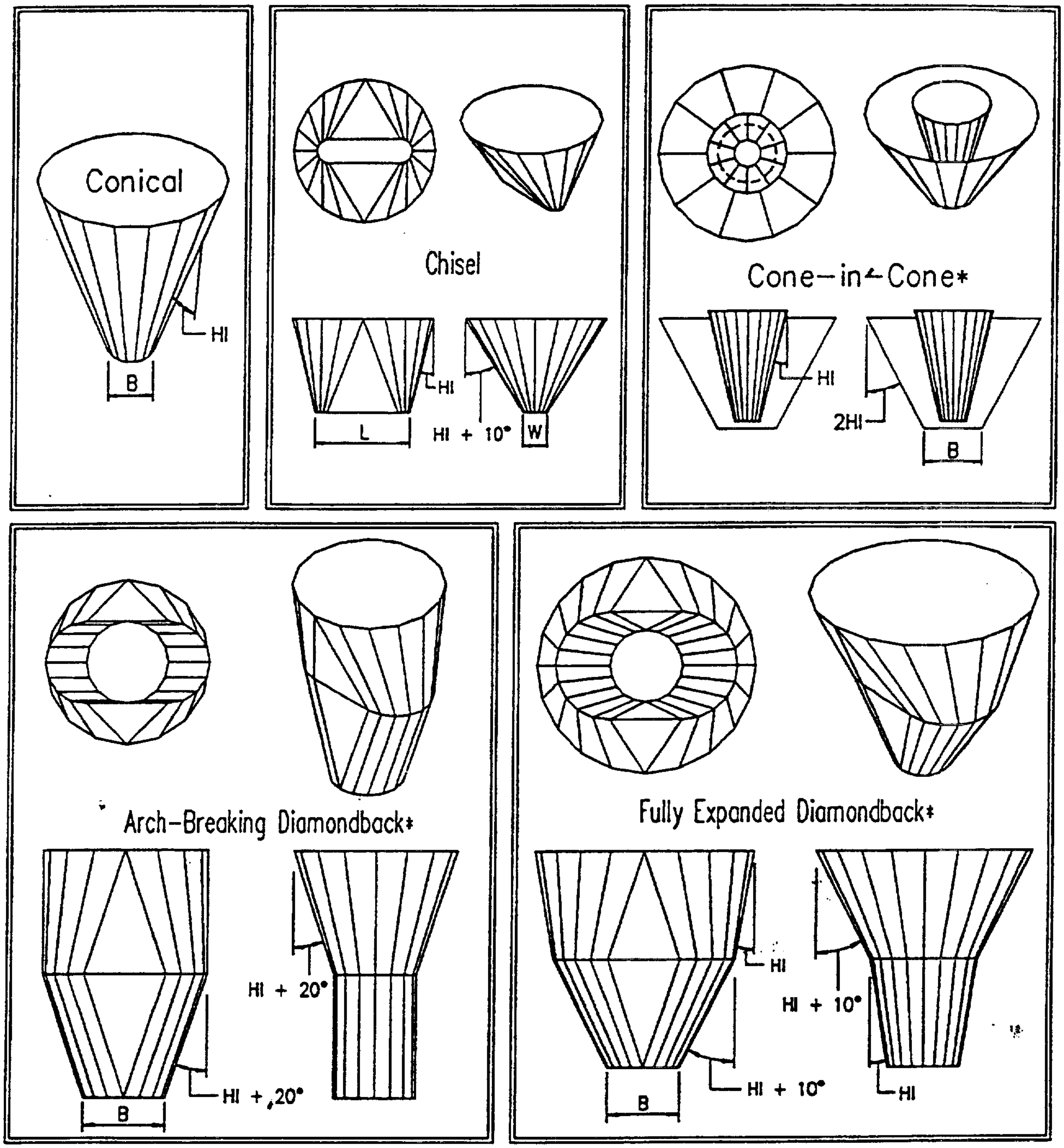
Rotary shell blenders

I will next consider how cohesive material properties affect rotating shell blenders such as twin cone, twin cylinder or cement mixers. These blenders attain their mixing action by solids sliding in thin layers down an angle of repose. The sliding action distributes a thin layer from the top across the entire length of the repose pile. This action is often implemented by some side-to-side mixing from lifter blades, converging shapes or stream splitting features. These blenders work best when the sliding region is very thin. The depth of the sliding layer is directly influenced by the hang-up properties of the solid. Chart I leads you through a decision tree to establish the cohesive solids influence on blending.

Chart I starts with determining the blender's size. Larger blenders tend to compact cohesive solids under high pressures; consequently, the rathole index more appropriately determines if the solids will slough off in large chunks and reduce blending efficiency. Other than this distinction, the left and right sides of the chart are essentially the same. They characterize blending in one of three categories: easy, difficult or try something different. The key factor in this decision tree is BL which depends on the size, fill, speed and geometry of the mixer. This must be determined either experimentally, estimated theoretically or a combination of both. Other blenders could also be analyzed in detail but this is outside the scope of this paper.

Table I
JOHANSON HOPPER INDEX HI INTERPRETATION

This index establishes safe-mass-flow hopper angles for various hopper configurations



*Cone-in-Cone Hopper U.S. Patent 4,286,833. U.K. Patent 2 056 296
Diamondback Hopper® U.S. Patent 4,958,741. Foreign patents pending.
Licenses for both products are available from JR Johanson, Inc., San Luis Obispo, CA.

Table II
Demixing Evaluation

Worst Mix	Type of Demixing and Description	Description of Materials Likely Causing Demixing				Best Mix
		Major Component		Minor Component		
		Description	Indices	Description	Indices	
90/10	**SIFTING** Free-flowing minor component particles sift through a bed of coarse, free-flowing major component particles.	•Free-flowing. •Three times or greater than the minor component.	AI<.2	•Free-flowing. •Particle size one-third or less than the major components.	AI<.2	50/50
70/30	**ANGLE OF REPOSE** The major component forms a steep angle of repose that causes the minor component with a lower angle or repose to slide to the bottom of the pile.	•Slightly less free-flowing than the minor. •Must have a higher angle of repose than the minor component.	.2<AI<1 (usually but not necessarily)	Free-flowing. • Any particle size.	AI<<.2	50/50
90/10	**FLUIDIZATION** Entrained air causes fines to fluidize and move like a liquid. Larger particles sink in the fluidized mass.	•Fine, fluidizable. •Not cohesive, at least when fluidized.	AI<.2 FRI<100	•Large. •Heavy. •Free-flowing.	AI<<.2 FRI>>100	60/40
90/10	**AIR CURRENTS** Super fine particles become airborne and collect at walls.	•Free-flowing. •Any size.	AI<.2	•Superfine. •Free-flowing.	AI<.2 FRI<<10	60/40

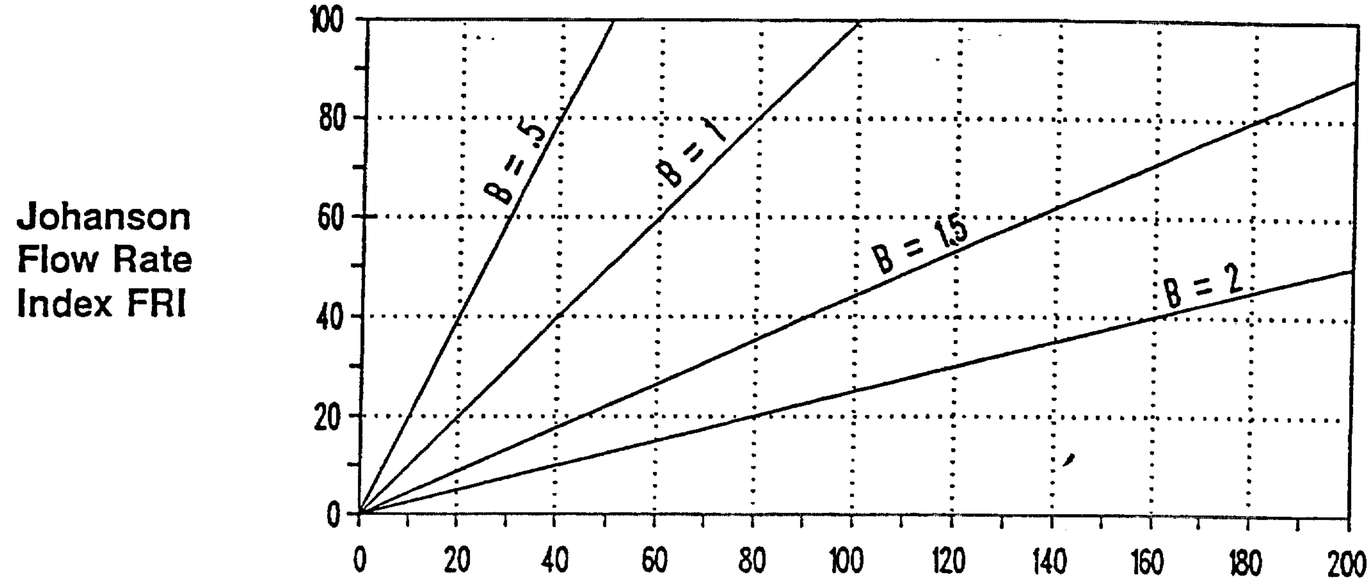
Table III
Various Blenders' Potential for Demixing

Blender Type	Demixing Mechansim							
	Sifting		Angle of Repose		Fluidization		Air Currents	
	Likely Rating	Controlled by	Likely Rating	Controlled by	Likely Rating	Controlled by	Likely Rating	Controlled by
Rotating Shell	High	Mass-flow discharge	High	Mass-flow discharge	Moderate	Low speed	Low	Low speed
Ribbon Blender	High	No good way	Moderate	Blender operating while discharging	High	Low speed	Moderate	Low speed
Rotating Plough	Moderate	Blender operating while discharging	Low	Not a problem	High	No good way	High	No good way
Screw Mixer	High	No good way	Moderate	Mass-flow discharge	Low	Not a problem	Low	Not a problem
Gravity Flow	Moderate	Anti-segregation distributor at top	Moderate	Anti-segregation distributor at top	Low	Not a problem	Low	Not a problem
Air Blender	High	No good way	Low	Not a problem	High	No good way	High	No good way

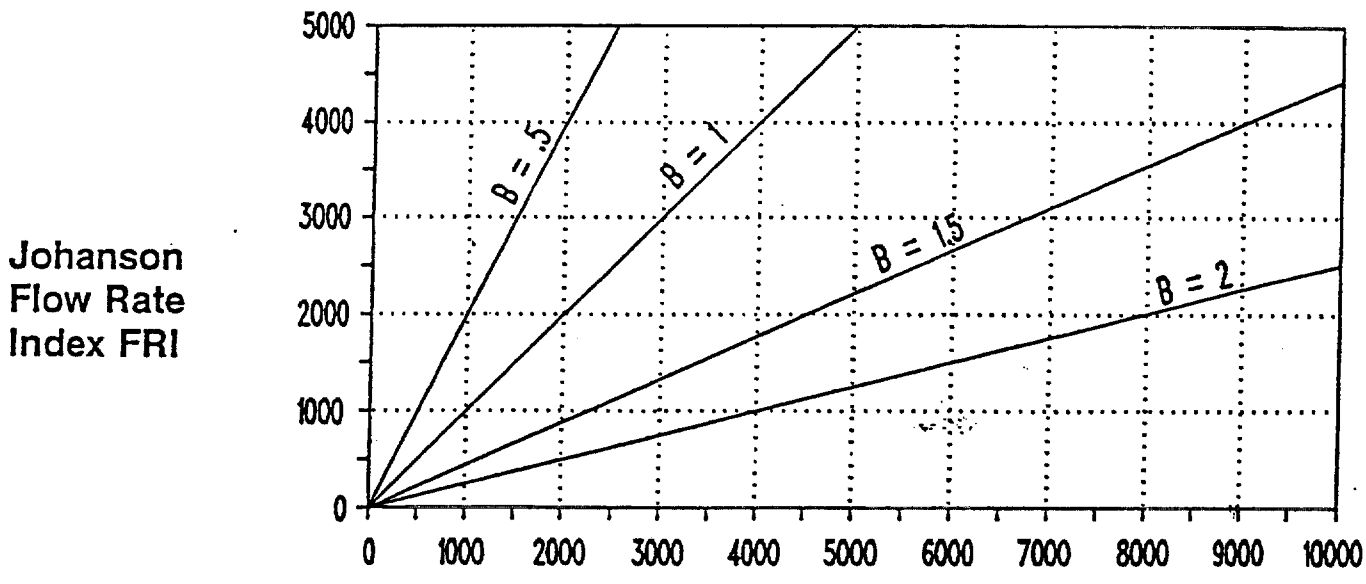
Table IV
Matching Blenders and Materials
Rating 1 to 10 with 10 being the best match

		BLENDER TYPES										
				Rotating Paddles		Screw Lift		Air Lift		Gravity Flow		
No	Particle size and Indices	Rotary Shell	Ribbon Blender	Vertical Shaft	Horizontal Shaft	Nauta Type	Central Screw	Bottom Pulse	Central Lift	Tube	Cone in Cone	Cylinder in Cylinder
1	Free-flowing, all components unform size AI<.2, RI<1, FRI>100	10	10	10	10	10	10	10	10	10	10	10
2	Same as 1 with large-sized major and small-sized minor components	2	3	4	5	2	3	2	3	5	8	8
3	Same as 2 with cohesive minor components	7	8	7	9	7	6	5	5	3	10	10
4	Same as 1 with small-sized major and large-sized minor components	3	6	8	8	8	8	7	7	7	9	9
5	Same as 4 with major components 1.5> AI>.6	6	7	9	9	8	6	3	2	2	9	9
6	Same as 4 with minor components 1.5> AI>.6	9	9	9	9	9	7	8	7	3	9	9
7	Major component easily fluidized AI<.2, RI<.2, FRI<10. Large, free-flowing minor component AI<.2, RI<2, FRI>100	7	5	2	4	7	6	3	2	2	4	9
8	Free-flowing major component AI<.2, RI<.2, FRI>50. Super fine, free-flowing minor component AI<.2, RI<4, FRI<2	7	7	5	7	9	8	3	3	7	7-9	7-9

FIGURE 1
Flow Rate Index Interpretation



Flow rate* (lb/min) for a deaerated solid at various conical hopper outlet diameters B (ft)



Flow rate* (lb/min) for a deaerated solid at various conical hopper outlet diameters B (ft)

*For slot openings length L, width B. Multiply the flow rate by 1.3 L/B.

FIGURE 2
Maximum Volumetric Flow Rates with Air Injection

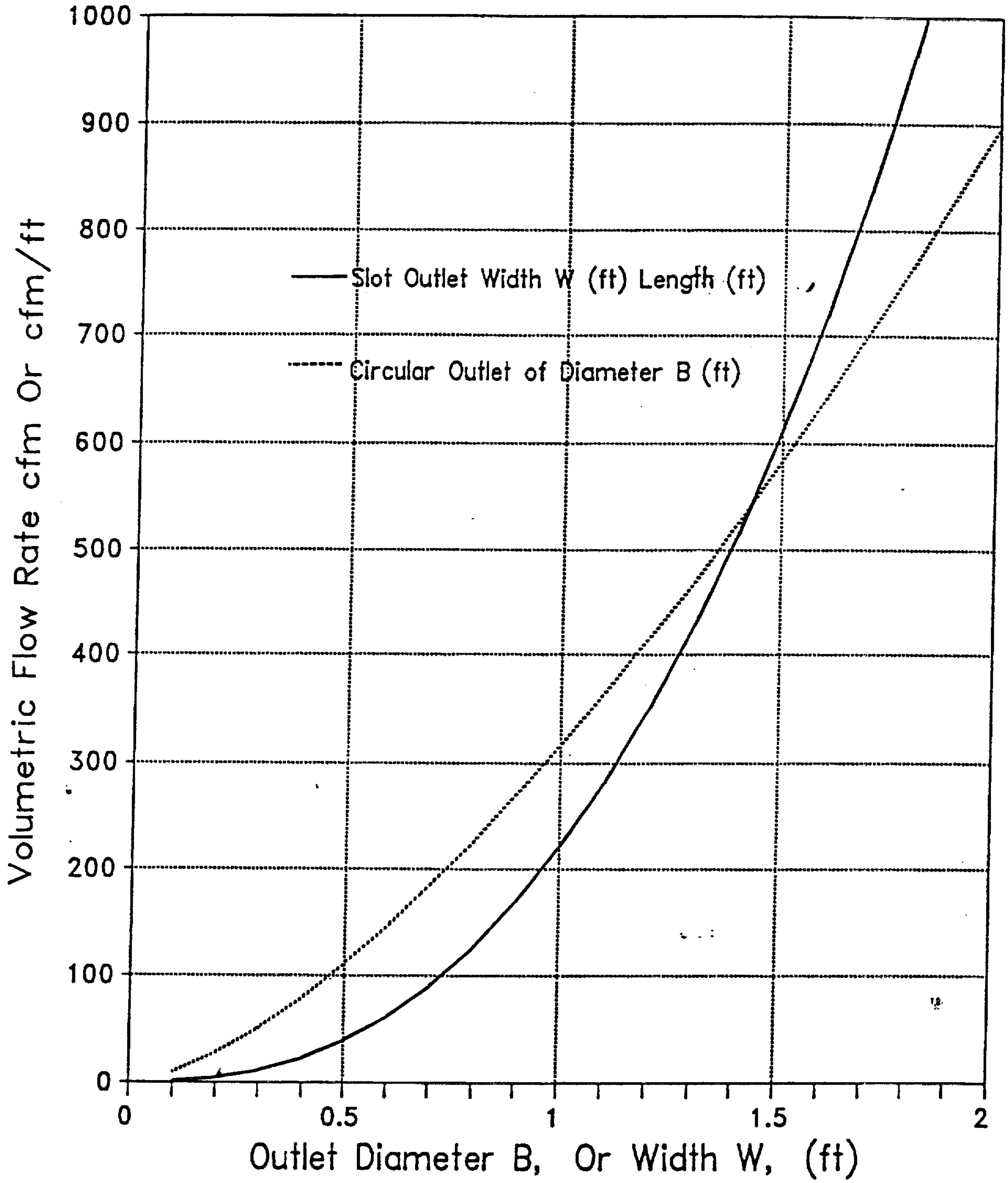
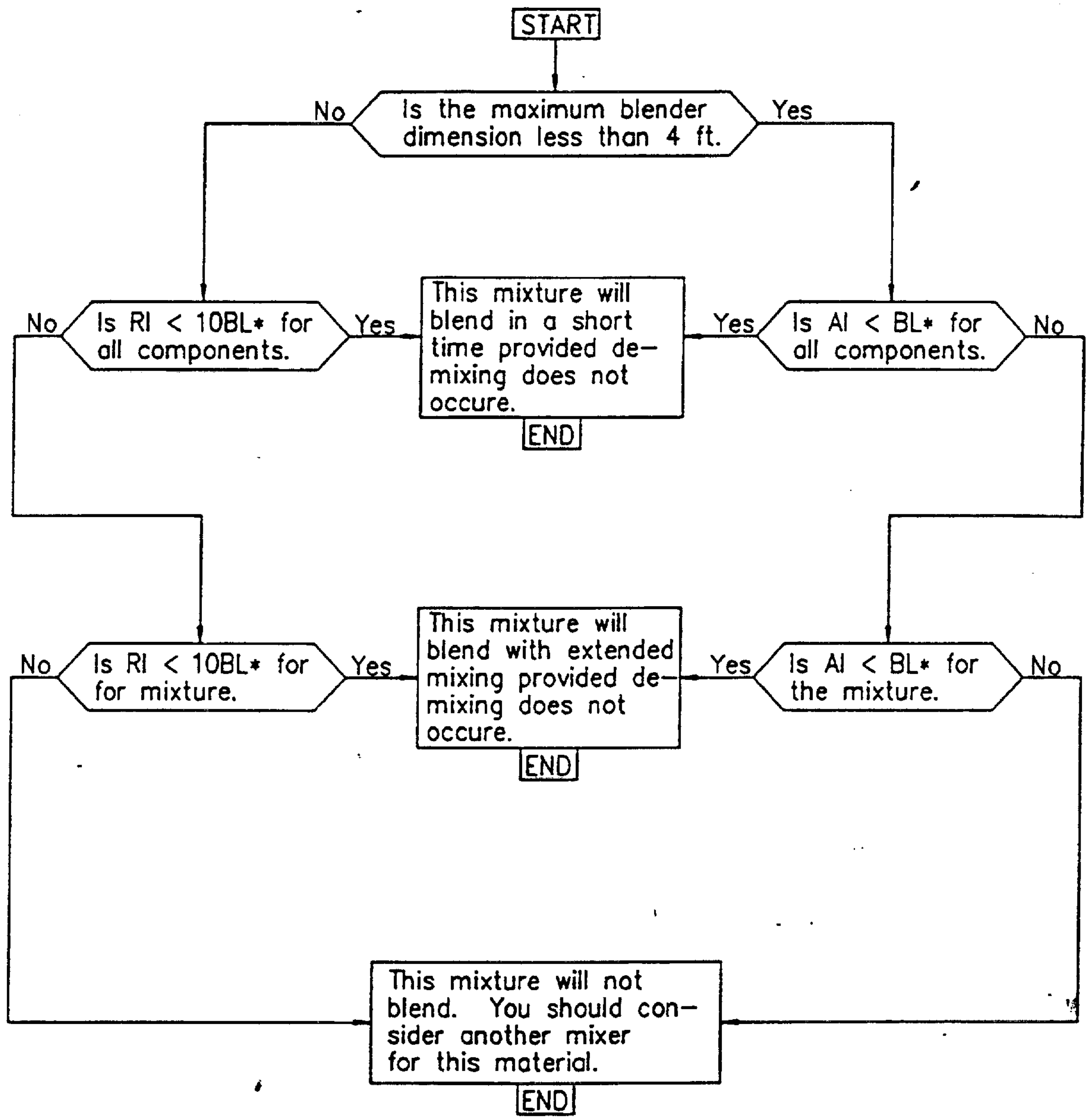


CHART I
Rotating Shell Blender Analysis



***BL** depends on the blender geometry, rotational speeds and degree of blending required. For a slow speed, twin-cone blender, **BL** is about 0.3.